



# Development of Taste-Masked Oral Reconstitutable Suspension of Cetirizine Dihydrochloride

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**Cetirizine dihydrochloride (CTZ) is a second-generation piperazine derivative, a potent H<sub>1</sub> selective antihistaminic agent. Its extreme bitter taste results in poor patient compliance. The aim of this study was to prepare taste-masked drug-resin complex (DRC) using ion exchange resin Kyron T-134. The DRC was evaluated for effect of variables such as resin ratio, pH, temperature, soaking time of resin, and stirring time on drug loading and taste. Reconstitutable suspension was prepared using drug-resin complex and other pharmaceutical excipients in suspension. Formulated reconstitutable suspension was evaluated for parameters before reconstitution, such as flow properties and drug content, and after reconstitution, such as aesthetic appeal, sedimentation rate, redispersibility, particle size, viscosity, pH, drug content, and *in-vitro* dissolution study. During the evaluation period of 14 days, no significant change was observed in pH, viscosity, particle size, and drug content. From the results, it is concluded that effective taste masking of CTZ was achieved using Kyron T-134 and successfully evaluated in reconstitutable suspension.**

A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium (1). FDA's Center for Drug Evaluation and Research (CDER) denotes reconstitutable suspension as "Powder, For Suspension", defined as an intimate mixture of dry, finely divided drugs and/or chemicals, which, upon the addition of suitable vehicles, yields a suspension (2). Reconstitutable suspension is reconstituted at the time of use and thus can be used as liquid formulation, which avoids swallowing problems. In aqueous solutions, many drugs degrade. Moreover, liquid product stability in tropical countries poses a great challenge because these products are exposed to elevated temperatures (up to 40 °C) and high relative humidity (up to 90%), especially during transport and storage (3,4).

Cetirizine dihydrochloride (CTZ) has a bitter taste and is prescribed extensively in both solid and liquid dosage forms for treating allergic conditions, including rhinitis and chronic urticarial (5). Its extreme bitter taste results in poor patient compliance in pediatric and geriatric patients. For these patients, drugs are commonly provided in liquid dosage forms, such as solutions, emulsions, and suspensions (6).

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stoichiometrically. They are available in desired size ranges. Bitter cationic drugs can get adsorbed onto the weak cation exchange resins of carboxylic acid to functionally form a complex that is non-bitter. Further, resinates can be formulated as lozenges, chewing gum, suspension, or dispersible tablets and can mask the taste (7,8). Drugs can be bound to the resin by either repeated exposure to or prolonged contact with the resin. Drugs are attached

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**Table I. Formulation of cetirizine dihydrochloride (CTZ) oral reconstitutable suspension.**

Ingredients	Functional category	mg/5 mL
Drug-resin complex (equivalent to 10mg/5 mL of CTZ)	Taste-masking drug	55
Xanthan gum	Suspending agent	30
Microcrystalline cellulose	Suspending agent	30
Propyl paraben	Preservative	20
Orange flavor	Flavor	25
Titanium dioxide	Opacifier	12
Sucrose	Filler	50

to oppositely charged resin substrates or resinates through weak ionic bonding so that dissociation of the drug-resin complex (DRC) does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs (9). The objective of this study was to mask the bitter taste of CTZ using ion exchange resin Kyron T-134 and check the feasibility of incorporating the DRC into reconstitutable suspension to increase patient compliance.

## Materials and method

**Materials.** CTZ was received from UCB India Private Limited (Vapi, India). The resin, Kyron T-134 (Batch no. 3009022), was procured from Corel Pharmachem (Ahmadabad, India). Xanthan gum, microcrystalline cellulose PH101, aspartame, sucrose, propyl paraben, and orange dry flavor were obtained from S.D. Fine Chemicals, Mumbai, India. Deionized distilled water was used throughout the study.

**Preparation of DRC.** DRCs were prepared by reacting CTZ with cation exchange resin Kyron T-134 in various stoichiometric ratios (1:1, 1:2, 1:3, 1:4, and 1:5). Kyron T-134 as weight ratio of the drug was placed in a beaker containing a required quantity of deionized water and allowed to swell. Accurately weighed CTZ was added to the solution and stirred. The mixture was filtered using Whatman filter paper, and residue was washed three times with 75-mL deionized water each time and dried. Drug in complex was calculated as drug-loading efficiency. DRC was optimized for various process conditions like drug-to-resin ratio, effect

of pH, effect of temperature, effect of soaking time of resin, and effect of stirring time (8,10).

## Evaluation of DRC

**Percentage yield.** Percentage yield of DRC was calculated by practical yield divided by actual theoretical yield (11).

**Drug content.** The CTZ content was determined by dissolving 100 mg of DRC with continuous stirring in 100 mL 0.1 N hydrochloric acid (HCl) (pH 1.2) for 4 h. The solution was filtered. After suitable dilution, the drug content was determined at 231.5 nm by ultraviolet-visible spectrophotometry (UV/Vis). The UV/Vis readings were taken in triplicate. Drug content was calculated using **Equation 1**:

Theoretical concentration of CTZ = 1000 µg/mL

$$\% \text{ drug content} = \frac{\text{practically obtained CTZ concentration}}{1000} \times 100 \quad [\text{Eq.1}]$$

**Physical properties of DRC.** Physical properties of DRC, such as particle size, angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were determined. All parameters were performed in triplicate (12,13).

**In-vitro drug release study.** Drug release from DRC (optimized drug: resin ratio of 1:3.5) in 0.1 N HCl was determined using a *United States Pharmacopeia (USP) XXIV* type II (paddle type) dissolution apparatus. DRC equivalent to 10 mg of drug was weighed accurately and added to 900 mL 0.1 N HCl and maintained at 37 °C. Drug release was performed at 100 rpm for 30 min. Five-milliliter samples were withdrawn after every five minutes up to 30 minutes. Samples were filtered with Whatman filter paper no. 41 and were analyzed at 231.5 nm by UV/Vis (12). The readings were taken in triplicate.

## Characterization of DRC

**Infrared study.** The drug, resin, and DRC were subjected to Fourier transform infrared (FTIR) studies to check any drug-resin interaction. FTIR spectra were recorded on samples prepared in potassium bromide using FTIR-8400S with infrared (IR) solution software (Shimadzu, Germany). Data were collected over a spectral region from 4000 cm<sup>-1</sup> to 400 cm<sup>-1</sup> (11).

**Preparation of oral reconstitutable suspension.** The oral reconstitutable suspension of CTZ was prepared from the optimized DRC. The formula is presented in **Table I**. All the ingredients for suspension were sieved through mesh no. 40 to make uniform particle size dispersion. The DRC equivalent to 10 mg/5 mL of suspension was mixed with the excipients. They were mixed properly to ensure uniform dispersion. Evaluation was performed on parameters before and after reconstitution (14,15).

**Evaluation of oral reconstitutable suspension.** Dry powder blend, ready for reconstitution, was evaluated for flow properties and drug content. After reconstitution, different pa-

**Table II. Preliminary trials for optimization of drug:resin ratio.**

Drug:resin ratio	% Drug loading
1:1	70.56±1.14
1:2	73.42±1.03
1:3	78.56±1.14
1:3.5	85.04±0.87
1:4	84.57±0.85

**Table III. Pre-reconstitution evaluation of dry powder blend.**

Test	Test results
Bulk density (gm/cc)	0.875
Tapped density (gm/cc)	0.983
Compressibility index (%)	11.41
Hauser's ration	1.12
Angle of repose (θ)	29.56
Drug content (%)	98.26±0.526

rameters, such as sedimentation volume, redispersibility of suspension, viscosity, pH, drug content, and *in-vitro* drug release study were evaluated (10,16).

**Sedimentation volume and redispersibility of suspension.** The formulated suspension was evaluated for physical stability by determining the sedimentation volume. Fifty milliliters of suspension was taken in a 100-mL stoppered graduated measuring cylinder. The suspension was dispersed thoroughly by turning the measuring cylinder upside down three times. Later, the suspension was allowed to settle for three minutes, and the volume of sediment was noted. This is the original volume of sediment ( $H_0$ ). The cylinder was kept undisturbed for 14 days. The volume of sediment was read at day 0, at day 7, and at day 14. The day 14 reading was considered the final volume of sediment ( $H_u$ ) (Equation 2). The redispersibility of the suspension was checked by repeatedly turning the stoppered cylinder upside down until there was no sediment at the bottom of the cylinder.

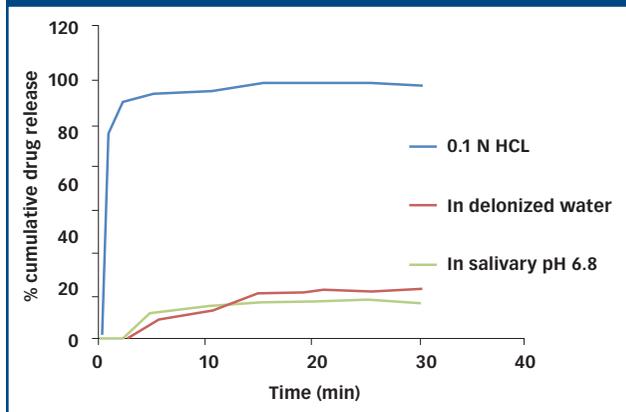
$$\text{Sedimentation volume} = \frac{H_u}{H_0} \quad [\text{Eq. 2}]$$

**Determination of viscosity.** A viscosity study was performed using a Brookfield viscometer DV-II+Pro, USA (Spindle no. S61). Viscosity was measured at 100 rpm, at 25 °C. The limits on viscosity were selected such that the suspension reached a physically stable state.

**pH of the suspension.** pH of the suspension was determined using a digital pH meter.

**Assay of suspension.** Five milliliters of suspension were taken in a 50-mL volumetric flask, and the volume brought up to 50

**Figure 1. *In-vitro* drug release profile of drug-resin complex in different dissolution media. HCl is hydrogen chloride.**



mL with 0.1 N HCL. The solution was sonicated for 30 min and filtered. Absorbance was then measured at wavelength 231.5 nm in UV-Vis, after which the percentage drug content was calculated.

***In-vitro* drug release.** *In-vitro* drug release of the suspension was performed using USP-type II dissolution apparatus (paddle type). The dissolution medium of 500 mL 0.1 N HCL was placed into the dissolution flask and temperature was maintained at 37±0.5 °C at 100 rpm. Five milliliters of suspension solution was placed in each flask of the dissolution apparatus. The apparatus was allowed to run for 35 minutes. Samples measuring 10 mL were drawn after every 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, and 35 min. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with 0.1 N HCL and analyzed at 231.5 nm using 0.1 N HCL as blank. The cumulative percentage drug release was calculated.

**Results and discussion**

**Drug loading.** As presented in Table II the complexation of drug with Kyron T-134 in a weight ratio of 1:3.5 gave efficient drug loading. The stirring time for all subsequent complexation processes was fixed to 4 h. Stirring time between 4 h and 5 h showed no significant change. The pH and temperature of solution did not show any significant effect on drug loading. Therefore, pH 4 and room temperature were selected for optimized batch preparation. No significant difference was observed when soaking time of resin in deionized water was changed from 30 min to 120 min. Thus, the soaking time of resin in deionized water was fixed to 30 min. Optimum conditions for the preparation of DRC were selected and used for further studies.

**Micromeritics.** The bulk and tapped densities were found at 0.613±0.013 and 0.674±0.016 g/cc, respectively. The compressibility between 5%–12% indicates excellent compressibility. The values of Hausner's ratio at less than 1.25% and angle of repose below 30° indicates good flowability.

***In-vitro* drug release from DRC.** Figure 1 demonstrates the drug release studies of CTZ from the DRC in 0.1 N HCL, phos-

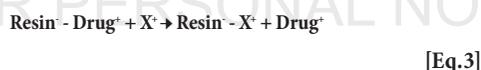
**Table IV. Sedimentation study of suspension.  $H_u$  is sedimentation volume at 14th day.  $H_0$  is original sedimentation volume at 0 day.**

Test	$H_u$	$H_0$	Sedimentation volume ( $H_u/H_0$ )
1 h	48	50	0.96
7 days	40	50	0.8
Hauser's ration	32	50	0.64
Angle of repose ( $\theta$ )		29.56	
Drug content (%)		98.26±0.526	

**Table V. Evaluation parameters of after-reconstitution oral suspension.**

Sample no.no	Test	0 day	7 days	14 days
1	Appearance	Uniform	Uniform	Uniform
2	Taste	Uniform	Uniform	Uniform
3	pH	6.8±0.1	6.7±0.1	6.7±0.1
4	Viscosity (cps)	56	52	50
5	Particle size	265±55	268±45	272±48
6	Drug content	98.45±0.521	98.012±0.865	98.32±0.601

phate buffer pH 6.8, and deionized water. In 0.1 N HCl more than 90% of drug release was achieved in 5 min, whereas in phosphate buffer pH 6.8 and deionized water, less than 20% drug release was achieved in 30 min. The exchange process of drug release is shown in **Equation 3**:



Where  $X^+$  represents the ions in the gastrointestinal tract.

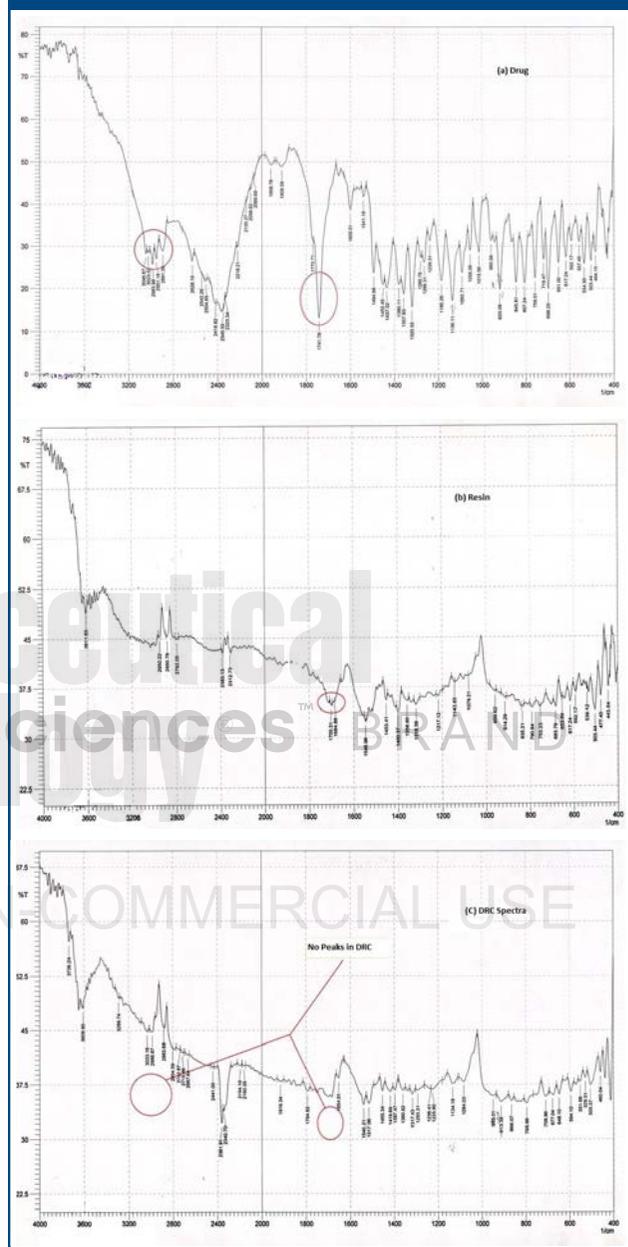
The presence of  $H^+$  ion in the 0.1 N HCl results in the displacement of CTZ, thus facilitating drug release. The amount of drug released was insufficient to impart a bitter taste in deionized water and phosphate buffer pH 6.8.

### Characterization of DRC

**FTIR spectroscopy.** The complexation was confirmed by IR studies. The absence of peaks at  $2323\text{ cm}^{-1}$ – $3046\text{ cm}^{-1}$  and at  $1741\text{ cm}^{-1}$  in DRC denotes complexation of drug and resin. The IR spectra of complex showed that there was no observed incompatibility between drug and resin. Peaks of both drug and resin were observed and interpreted (**Figure 2**).

**Reconstituted suspension.** Prepared suspension was evaluated for flow properties and drug content before reconstitution. Results are shown in **Table III**. Results showed that the reconstitutable blend has excellent flow properties and optimum drug content, and that the prepared blend had good dispersion homogeneity. At the time of use, the reconstitutable blend was reconstituted with water for preparation of suspension.

**Figure 2. Fourier Transform infrared spectra of (a) cetirizine dihydrochloride, (b) Kyron T-134, and (c) drug-resin complex.**



**Sedimentation volume of suspension.** The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. In prepared formulation, there was little sedimentation after 7 days and 14 days, and the particles could be easily redispersed. Moreover, uniform dispersion was achieved after a minimum number of strokes. Results are shown in **Table IV**.

Sedimentation rate depends on the viscosity of the medium. From sedimentation volume data, it can be seen that suspension is stable and easily redispersed after 14 days. Thus, the viscosity of the suspension is sufficient to keep the suspension stable.

The reconstitutable blend for suspension was subjected to stability studies for a period of 14 days. The samples were reconstituted in purified water to formulate a suspension. This was analyzed for pH at day 0, day 7, and day 14 after reconstitution. There was no appreciable change observed in pH and drug content. Size of the particles in suspension was reasonably constant even after 14 days. This indicated no crystal growth. Results are shown in **Table V**.

**In-vitro drug release.** Drug release from the prepared formulation was observed in 0.1 N HCl. Results showed that nearly 85% of drug release was found from prepared suspension in duration of 5 minutes. This is happened because drug in form of DRC is weak enough to be broken down at gastric pH 1.2 and allow the rapid release of drug from suspension.

## Conclusion

In the present study, an attempt was made to mask the bitter taste of CTZ by using Kyron T-134 as an ion exchange resin. Various parameters affecting taste masking, such as resin ratio, pH, temp, soaking time of resin, and stirring time were optimized with efficient loading of drug. The nature of the DRC is such that the average pH of 6.8 in saliva is not able to break the complex. *In-vitro* drug release in salivary pH of 6.8 was less than 5% within 60 s. Ideally, an oral suspension is swallowed by a patient in a fraction of that time (not more than 60 s). Yet, the DRC is weak enough to be broken down at gastric pH 1.2, thus the complex is considered absolutely tasteless in salivary fluid. Taste-masked DRC has shown excellent flow properties in this study. Furthermore, formulated CTZ reconstitutable suspension has acceptable sedimentation properties. In a 14-day evaluation period, it is observed that no significant change was observed in pH, viscosity, particle size, and drug content. This method is simple and cost effective to prepare taste-masked reconstitutable suspension of CTZ that may be acceptable to the industry.

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